Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension: A retrospective study of 75 paediatric cases [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Ventricular septal defects (VSD) are the second commonest congenital heart defects after bicuspid aortic valve. When left unrepaired, they can undergo spontaneous closure or elicit a spectrum of complications including pneumonia (PNA) or pulmonary hypertension (PH) with subsequent anaemia. In this retrospective study, we aim to establish and compare the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods: A total of 75 case files of patients with solitary acyanotic VSD, who underwent surgical closure or device occlusion had haemoglobin level analysed prior to the procedure. The cohort included patients with (history of) PNA and PH, and asymptomatic. The cohort included 27 females and 48 males with mean age and weight of 8.3±5.72 (3-24) months and 5.9±3.9 (2.7-17.8) kilograms, respectively. Depending on associated complication and age, the cohort was divided: PNA (A), PH (B) and Control (C); and (I) young children (≥3-6≤) and (II) older children (>6-≤24) months. We used 95 and 105 grams per litre as haemoglobin lower threshold level for (I) and (II), respectively.

Results: According to data analysis 27 patients (36%) in total had anaemia. Of the anaemia cohort 16 (59.3%) had PNA, 9 (33.3%) PH and 2 (7.4%) were asymptomatic. Of the cohort, 42 were young children, with anaemia prevalence of 19/42 (45.2%), while 24.2% of the older children had anaemia. Intergroup ANOVA independent sample t-test was significant (p<0.05). In addition, intergroup Tukey HSD test for haemoglobin: A/B (p>0.05), A/C (p<0.01), B/C (p<0.01).

Conclusion: Paediatric patients with acyanotic VSD in comorbid with PNA or PH are 8 and 4 times more susceptible to develop anaemia compared to asymptomatic counterparts. Susceptibility is even higher among young children (3-6months). However, a prospective study is needed to validate our findings.
Keywords
Ventricular septal defect, Pneumonia, Pulmonary hypertension, Anaemia

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Author roles: Changwe GJ: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; Zhang H: Methodology, Resources; Li H: Formal Analysis, Supervision; Farhaj Z: Data Curation, Methodology; Tewara MA: Formal Analysis, Software; Zhang W: Validation, Visualization; Zou C: Funding Acquisition, Project Administration, Validation

Competing interests: No competing interests were disclosed.

Grant information: Funding for this project was provided by Shandong University PR China; and National Key R & D program of P.R. China (Grant no. 2017YFC1308000)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Changwe GJ, Zhang H, Li H et al. Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension: A retrospective study of 75 paediatric cases [version 1; peer review: 1 approved with reservations] F1000Research 2019, 8:101 (https://doi.org/10.12688/f1000research.17907.1)

Introduction

Anaemia is a common complication of a myriad medical conditions often met in general ward. Its etiology is complex and multifactorial, encompassing intrinsic and extrinsic factors\(^1\). Cyanotic congenital heart defects are known to severely derail smooth blood flow with subsequent iron homeostasis dysregulation. Prevalence of anaemia amongst patients with cyanotic VSD is known and well documented in a variety of world literature\(^2\). On the contrary, solitary acyanotic ventricular septal defect (VSD) exhibit a relatively smooth blood with unremarkable iron homeostasis dysregulation. However, depending on size and duration, solitary VSD can lead to pulmonary hyper-circulation with subsequent complications, including recurrent lower respiratory tract infection (pneumonia; PNA), pulmonary hypertension (PH), pulmonary vascular disease, heart failure and death\(^3\).

PNA is known to cause local hypoxia with subsequent upregulation of erythropoiesis. In addition, certain causatives of PNA are known to compete for iron with the host, whereas others induce haemolysis, both leading to anaemia\(^4\). Equally, PH has been associated with severe forms of haemolytic anaemia in patients with haemoglobin disorder and erythrocyte membranopathies\(^5,6\). In addition, free haemoglobin produced as a result of haemolysis depletes nitric oxide with subsequent vessel constriction, local hypoxia and exacerbation of PH\(^7\). Both PNA and PH exhibit tendencies of inducing local hypoxia, leading to upregulation of erythrocyte synthesis. Adults and older children with enough iron store can tolerate such a condition without developing anaemia. However, infants and young children have inadequate iron stores. In addition, children below the age of 6-months fed exclusively on breast milk have limited source of iron replacement. For the reasons mentioned above, we hypothesize that paediatric patients with solitary acyanotic VSD coexisting with PNA or PH retain a risk of developing anaemia. In this retrospective study, we aim to establish the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods

Case file details and classification

Between February 2014 and September 2018, 90 case files of patients with solitary acyanotic VSD, who underwent either surgical or minimal invasive closure in our Department of Cardiac Surgery, Shandong Provincial Hospital Affiliate of Shandong University were primarily selected for this study.

However, only 75 case files met study criteria, which included patients with a history of proven PNA by chest radiography with positive bacterial culture of trans-tracheal aspirate or polymerize chain reaction from nasopharyngeal swab. Pulmonary hypertension diagnosis was echocardiography based, except in 5 patients from PNA group, who presented in heart failure state. Excluded from this study were 15 files of patients: 7, sickle cell; 4, β-Thalassemia; 4, blood transfusion.

Among the 75 files were 48 males (75.64%) and 27 females with mean age and weight of 8.3±5.7 (3–24) months and 3.8±3.0 kilograms, respectively. Depending on the associated complication, the cohort was then divided into three groups: A, PNA (n=30); B, PH (n=25); and C, control (n=20). Based on age, the cohort was further split into two groups: I, young children (≥3≤6); II, older children (>6≤24) months. The patient demographic and clinic characteristics (Table 1) and hematologic profile (Table 2) reflects pre-procedure state.

Data variables

Statistical analysis. Data was analysed using IBM SPSS-software (one-way-ANOVA) and all statistics expressed as mean ± standard deviation. Intergroup haemoglobin level was compared using independent samples student’s t-test. Statistical comparison of proportions was analysed using Tukey HSD Test, and the probability value of less than 0.05 was considered significant. Patient proportions are expressed in number and percentage (n, %).

Results

In this study, the haemoglobin reference range for groups: I and II were (95–135g/L) and (105–135g/L) respectively. This thus, conforms with local protocol.

According to data analysis in Table 3, 27 patients (36%) in total had anaemia. Of the anaemia cohort, 16 (59.3%) had PNA, 9 (33.3%) had PH, and 2 (7.4%) were asymptomatic. These results can be expressed as ratios 16:9:2=8:4.5:1; therefore,

### Table 1. Patient demography and clinical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>N</td>
<td>75</td>
<td>30</td>
</tr>
<tr>
<td>Age, months, mean± SD</td>
<td>8.3±5.72 (range, 3–24)</td>
<td>10.8±19</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>27/48</td>
<td>9/21</td>
</tr>
<tr>
<td>Weight, kgs, mean±SD</td>
<td>5.9±3.9 (range, 2.7–17.8)</td>
<td>4.9±3.2</td>
</tr>
<tr>
<td>Ventricular septal defect, cm, mean±SD</td>
<td>0.93±0.31 (range, 0.4–1.6)</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Pulmonary hypertension, mmHg, mean±SD</td>
<td>25.5±8 (range, 16–55)</td>
<td>21.2±3.4</td>
</tr>
</tbody>
</table>
patients with PNA and PH are 8 and 4 times more susceptible to developing anaemia than asymptomatic patients.

Of the cohort, 42 were young children, and of those 19 had anaemia (45.2%), while 24.2% of the older children had anaemia. Haemoglobin intergroup (ANOVA) independent sample t-test was significant (p<0.05). In addition, intergroup Tukey HSD test for haemoglobin: A/B (p>0.05), A/C (p<0.01), B/C (p<0.01).

The mean white blood cells in patients with PNA was higher and intergroup p-value was significant (p<0.05).

Discussion

Anaemia, defined as haemoglobin (Hb) concentration below the 5th percentile for age at sea-level, is a common complication of a myriad medical conditions often met in the general ward. Its aetiology is complex and multifactorial, encompassing intrinsic and extrinsic factors. Both pneumonia (PNA) and pulmonary hypertension (PH) due to cyanotic congenital heart defect (CHD) have been implicated in the occurrence of anaemia. Sporadic reports linking anaemia to PNA or PH amongst patients with acyanotic ventricular septal defect (VSD) have been publish.

VSD is the second commonest CHD after bicuspid aortic valve, and solitary cases account for almost 20%. One of the most common defects associated with elevated pulmonary artery pressure is a large VSD. Elevated pulmonary artery pressure in CHD can be due to pulmonary hyper-circulation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination. In an infant, despite pulmonary pressure being at systemic level, pulmonary vascular resistance is low; therefore, minor shunt easily elicits hyper-circulation.

PH, defined as mean pulmonary artery pressure of ≥25mmHg at rest as measured by cardiac catheterization in children aged ≥3months, is a serious disorder with a high morbidity and mortality rate. Blood shunt may cause haemolysis due to shear stress and produce free haemoglobin, which in turn depletes nitric oxide leading to endothelial dysfunction, vasoconstriction,

Table 2. Mean hematologic profile and laboratory results according to age groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young children (≥3–≤6months; n=42)</th>
<th>Older children (&gt;6–≤24 months; n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A+</td>
<td>B+</td>
<td>C+</td>
</tr>
<tr>
<td>Haemoglobin (g/l; mean±SD)</td>
<td>109±25.1</td>
<td>108.3±21.2</td>
<td>132.2±18</td>
</tr>
<tr>
<td>Mean corpuscular volume (f/l)</td>
<td>76.9±7.3</td>
<td>85.7±2.1</td>
<td>83.9±9</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin (pg; mean±SD)</td>
<td>27±3.1</td>
<td>30.3±2.1</td>
<td>28.4±1.8</td>
</tr>
<tr>
<td>Lactate dehydrogenase (mean±SD)</td>
<td>236.8±76.8</td>
<td>222.4±61.6</td>
<td>213.6±16</td>
</tr>
<tr>
<td>White blood cell (×10⁹/L; mean±SD)</td>
<td>12.5±5.3</td>
<td>7.8±2.4</td>
<td>6.9±0.9</td>
</tr>
<tr>
<td>Red blood cell (×10¹²/L; mean±SD)</td>
<td>3.8±0.9</td>
<td>3.6±0.9</td>
<td>3.8±0.4</td>
</tr>
</tbody>
</table>

Table 3. Association between age and anaemia prevalence.

<table>
<thead>
<tr>
<th>Group</th>
<th>N; age (months; mean±SD)</th>
<th>Haemoglobin (%)</th>
<th>Anaemia</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young children (≥3–≤6months; n=42)</td>
<td>19; 4.85±1.07</td>
<td>45.2</td>
<td>54.8</td>
<td></td>
</tr>
<tr>
<td>Older children (&gt;6–≤24months; n=33)</td>
<td>6; 12.69±6.02</td>
<td>18.2</td>
<td>81.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Association between complication and anaemia distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>
pulmonary oedema and hypoxia. Furthermore, haemolysis produces arginase, which converts L-arginine to ornithine; therefore, bypassing nitric oxide production.\textsuperscript{2,3,12}

PNA, defined as an inflammation of alveoli (with or without pus) due to an infection is a serious morbidity and mortality reason for children (≤2years) with hemodynamic significant VSD.\textsuperscript{3,11} Similar to PH, inflammatory state in PNA causes pulmonary oedema, homeostasis and hypoxia, with subsequent upregulation of erythrocyte synthesis.\textsuperscript{4,14} Prolonged upregulated erythropoiesis in young children with low iron store and limited iron source (exclusive breast milk) can develop low haemoglobin levels.\textsuperscript{1} In addition, microangiopathic haemolytic anaemia in CHD and PH has been reported,\textsuperscript{1} a complication commonly observed in primary PH. Unlike PH, a number of PNA causatives are known to cause haemolytic and iron deficient anaemia. \textit{Mycoplasma pneumoniae} has been reported to cause severe haemolytic anaemia.\textsuperscript{3,16} In addition, \textit{Klebsiella} is known to compete for iron with host via siderophores.\textsuperscript{6}

Our study shows that patients with acyanotic VSD within mean sizes 1.2±0.3 and 0.89±0.2 cm were prone to develop recurrent lower respiratory tract infection and pulmonary vascular disorder. The two pathological conditions primarily share common features including pulmonary oedema, haemostasis and hypoxia, with an immediate non-hemodynamic response in form of increased erythropoiesis. However, unlike PH, toxins from certain causatives (bacteria) in PNA induce haemolysis, while other pathogens compete for iron with the host. Owing to LDH and WBC elevation in group A, it is evident that there was some haemolysis of a certain degree as a result of an infection. Other potential causes include microangiopathic haemolysis in CHD with PH, feeding difficulties and malabsorption. Given the high proportion of anaemia in the ‘young children’ group, it is logical to assume they were fed exclusively on breast (artificial) milk, possibly limiting the source of iron. From our study, it is evident that diagnosis of hemodynamic significant acyanotic VSD in comorbid with PNA or PH should heighten the suspicion index of anaemia. However, we acknowledge that aetiology of anaemia is multifactorial, and so many intrinsic and extrinsic factors are at play, hence, every case requires a holistic approach.

**Limitations**

To the best of our knowledge this comparative concept is new; therefore, a larger cohort in a prospective model would validate our findings.

**Conclusion**

Paediatric patients without hematologic disorders, diagnosed with hemodynamic significant acyanotic VSD in comorbid with PNA or PH are 8 and 4 times susceptible to develop anaemia compared to asymptomatic counterparts. Susceptibility is even high amongst young children (3–6months).

**Ethical considerations**

The Shandong Provincial Hospital Ethics Committee approved this study, and waived individual patient consent as the study was based on archived data.

**Data availability**

Harvard Dataverse: Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension; a retrospective study of 75 paediatric cases, https://doi.org/10.7910/DVN/2B328D.\textsuperscript{15}

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Grant information**

Funding for this project was provided by Shandong University PR China; and National Key R & D program of P.R. China (Grant no. 2017YFC1308000).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Acknowledgements**

We thank the management and staff of the Department of Cardiovascular Surgery and Imaging of Shandong Provincial Hospital, affiliated to Shandong University.

**References**

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http://www.doi.org/10.7910/DVN/2B328D
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Current Peer Review Status:  

Version 1

Reviewer Report 27 March 2019

https://doi.org/10.5256/f1000research.19583.r44745

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Shengli Li
Department of Ultrasound, Shenzhen Maternity and Child Healthcare Hospital, Southern Medical University, Shenzhen, China

1. The manuscript is a small-size retrospective study about the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH; they find that patients with acyanotic VSD in comorbid with PNA or PH were 8 and 4 times more susceptible to develop anaemia compared to asymptomatic counterparts.

2. For the VSD patients with PNA or PH, does the increased incidence of anaemia have any influence on the therapy or clinical management?

3. As the aetiology of anaemia is multifactorial, any intrinsic and extrinsic factors should be analysed in this article. This is crucial.

4. As mentioned above, it suggests that this article needs to be revised before accepting for indexing.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes
Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Fetal medicine, prenatal diagnosis of fetal malformations

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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